# Chickenpox Encephalitis and Encephalopathy: Evidence for Differing Pathogenesis

THOMAS C. SHOPE, M.D.

*Division of Infectious Diseases, Children's Hospital of Michigan, and Department of Pediatrics, Wayne State University, Detroit, Michigan*

Retrospective assessment of hepatic and central nervous system involvement associated with chickenpox cases at a large metropolitan medical center reveals that 28 of 58 patients had biochemical, but not inflammatory, evidence of liver involvement. An additional 18 patients had biochemical liver abnormalities along with non-inflammatory encephalopathy (Reye syndrome) and 12 had clear evidence of central nervous system inflammatory involvement (encephalitis). There were no cases of solitary inflammatory liver involvement. Reviewed evidence suggests that the pathogenesis of hepatopathy and hepatoencephalopathy (Reye syndrome) is not caused by replication of virus in the involved organs, but instead is mediated through a cytotoxic mechanism and that the inflammatory brain disease is also not caused by viral replication in brain tissue, but appears to be tissue damage associated with immune cell responses (post-infectious encephalitis). The concept put forth in this essay is that a virus replicating in one organ (skin) could affect the macromolecular function of cells in another organ (liver, brain) bringing about both hepatopathy and hepatoencephalopathy.

Varicella-zoster virus (VZV) causes chickenpox, a common childhood infectious disease which is self-limiting and not usually associated with secondary complications. Occasionally, however, serious complications are associated with VZV infection. Fulminant systemic disease, sometimes fatal, can occur in immunocompromised and newborn patients [1-3]. In the immunocompetent person, thrombocytopenia [4], varicella pneumonia [5,6], and a variety of central nervous system conditions including cerebellar ataxia and encephalitis have been described [7,8]. Though rare, the highly publicized Reye syndrome has been associated with preceding chickenpox in 4-20 percent of cases [9-12]. And finally, there is increasing mention in the medical literature of varicella hepatitis, particularly in relation to varicella-associated Reye syndrome [13-15]. The purpose of this essay is twofold: first, to report the recent experience with hepatic and encephalitic involvement during chickenpox among patients admitted to a large metropolitan pediatric hospital, and, second, to utilize data in this study and others to speculate on the pathogenesis of hepatic and encephalitic conditions associated with chickenpox.

## METHODS

A retrospective chart review from inpatients at the Children's Hospital of Michigan-Wayne State University medical complex was conducted covering a period from January 1978 through July 1981. Charts from patients with chickenpox, Reye

Address reprint requests to: Thomas C. Shope, M.D., F-2815, Box 66, C.S. Mott Children's Hospital, University of Michigan Medical Center, Ann Arbor, MI 48109

syndrome with chickenpox, hepatitis, encephalitis, and cerebellar ataxia were reviewed. The purpose of the review was to detail the signs and symptoms, illness severity and duration, and laboratory test results found in patients who had chickenpox-related sequelae involving the liver and/or brain. Based on these characteristics, cases were assigned to one of three categories: hepatopathy, hepatoencephalopathy, or encephalitis. Patients assigned to the *hepatopathy* case category had clear evidence of biochemical derangement of liver cells with elevated liver enzyme blood levels but normal bilirubin and alkaline phosphatase levels. Signs of possible cerebral origin, such as lethargy, headache, and irritability were permitted, but if a child's condition included signs or symptoms more distinctive of Reye syndrome, the case was placed in the hepatoencephalopathy category. Patients were assigned to the *hepatoencephalopathy* (Reye syndrome) case category when there was clear evidence of biochemical derangement of liver cells with elevated liver enzyme blood levels (but normal bilirubin and alkaline phosphatase levels) as well as signs of cerebral dysfunction consistent with the following Reye syndrome classification stages: Stage I, disorientation; Stage II, combativeness; Stage III, coma; Stage IV, decerebrate posturing; and Stage V, flaccid paralysis [16]. Finally, patients assigned to the *encephalitis* case category had clear signs of either cerebellar neurologic derangement or cerebral neurologic dysfunction or inflammation such as seizure or meningismus.

## RESULTS

In the 3.5-year period studied, 58 cases of chickenpox-associated sequelae of the liver and/or brain were found. Persistent emesis (greater than three episodes) was present in 55 of the 58 children (95 percent) regardless of final case category. Table 1, comparing the three case categories, presents the relative frequency of symptoms

TABLE 1
Presenting Symptoms Among Children with Liver and/or Brain Sequelae During Chickenpox

| Hepatopathy n = 28 | | Hepatoencephalopathy n = 18 | | Encephalitis n = 12 | |
|---|---|---|---|---|---|
| Lethargy | 8† | Lethargy | 6 | Unsteady gait | 7 |
| Headache | 6 | Restless | 3 | Headache | 6 |
| Irritability | 3 | Irritability | 2 | Lethargy | 3 |
| Restless | 1 | Headache | 1 | Meningismus | 2 |
| Listless | 1 | Listless | 1 | Seizure | 2 |
|  |  |  |  | Agitation | 1 |
| Emesis and at least one of the above | 14 | Emesis and at least one of the above | 11 | Emesis and at least one of the above | 10 |
| Emesis only | 13 | Emesis only | 7 | Emesis only | 0 |

*Final Reye Stage*

| | | |
|---|---|---|
| I | Disoriented | 2 |
| II | Combative | 11 |
| III | Coma | 1 |
| IV | Decerebrate | 3* |
| V | Flaccid | 1* |

†Frequency
*One death each

which occurred within four days prior to the day of admission (in most the symptoms occurred within two days of admission). Patients in the two cytotoxicity categories, hepatopathy and hepatoencephalopathy, reported symptoms only vaguely suggestive of neurologic imbalance during the period of illness prior to presentation to the hospital. Indeed, 20 of the 46 children experienced only persistent emesis before either recovery or progression into symptoms attributable to increased intracranial pressure and encephalopathy. In contrast, the 12 children with inflammatory brain involvement developed signs or symptoms of neurologic disturbance such as ataxia, seizure, or meningismus prior to presentation at the hospital. There are no children who presented with signs or symptoms clearly suggestive of primary hepatitis.

Results of examination of spinal fluid for leukocytes are presented in Table 2. Spinal fluid cell counts were normal for all patients examined in the two cytotoxicity categories. In contrast, spinal fluid pleocytosis was present in seven of 10 patients with inflammatory brain involvement. The presence of cerebrospinal fluid (CSF) pleocytosis in the encephalitis group appears to support separation of that group of patients from the other two groups.

Finally when the case categories are compared by duration of selected aspects of their illness, as in Table 3, two significant differences emerge. Total duration of illness was significantly shorter in the hepatopathy group of children than either of the other two categories, a result which supports separation between the cases in the hepatopathy group from those in the hepatoencephalopathy category. And the day of onset of the complication was significantly later among those with encephalitis than in either cytotoxicity category, suggesting similar pathogenesis for the cytotoxic cases and a different pathogenesis for the encephalitis category of patients.

## DISCUSSION

With respect to the liver and brain, three distinct pathologic processes leading to cell damage appear to occur in association with varicella infection: a non-inflammatory cytotoxicity, destruction of cells by direct virus infection, and destruction of cells through inflammatory cell responses. In the first condition, damage to cells is best characterized as cytotoxic. Histopathology includes fatty metamorphosis in liver cells and generalized edema of brain tissue. There is striking absence of inflammatory cell response and no evidence of viral replication in affected cells. The cause remains perplexing but, when recovery occurs, the altered cell process resolves without evident permanent damage to the involved cell. In the second condition, destruc-

TABLE 2

Spinal Fluid Leukocytes Among Children with Liver and/or Brain Sequelae During Chickenpox

| | Hepatopathy $n = 28$ | Hepatoencephalopathy $n = 18$ | Encephalitis $n = 12$ |
|---|---|---|---|
| Abnormal > 8 cells | 0 | 0 | 7* |
| Normal ≤ 8 cells | 4† | 11† | 3△ |
| Not examined | 24 | 6 | 2 |
| Traumatic | 0 | 1 | 0 |

*Range 15-167 cells (mean, 53), 3-28 segmented cells (mean, 13)
†Range 0-6 cells, no more than one segmented
△Two cases with ataxia, one with meningismus

TABLE 3
Comparison of Selected Aspects of Illness Among Children with Liver
and/or Brain Sequelae During Chickenpox

| | Hepatopathy $n = 28$ | Hepato/encephalopathy $n = 18$ | Encephalitis $n = 12$ |
|---|---|---|---|
| Mean days ill | 3.4 ± 1.9* | 9.7 ± 13.9 | 8 ± 4.9 |
| (range) | (1–10) | (3–63) | (1–16) |
| Mean days of emesis before admission | 1.2 ± 1.0 | 1.8 ± 0.9 | 1.0 ± 1.0 |
| (range) | (0–4) | (0–3) | (0–3) |
| Mean day of onset after chickenpox rash | 3.7 ± 3.0 | 3.5 ± 1.7 | 5.8 ± 3.3† |
| (range) | (2–6) | (1–8) | (1–12) |

*$p < 0.003$ (Student $T$-test)
†$p < 0.02$ (Student $T$-test)

tive damage to cells follows in situ viral replication. Histopathology includes areas of focal necrosis, cells with intranuclear inclusions, and usually an associated inflammatory cell reaction. In this setting, recovery may occur but usually not without evidence of permanent cell damage or loss. Finally, in the third condition, cell damage results from a post-infectious inflammatory cell infiltration of the diseased tissue with no evidence of viral replication. The first condition is usually referred to with words ending in "pathy," the latter two conditions, with words ending in "itis." Thus hepatopathy and encephalopathy are terms used to describe conditions where cell damage occurs without the usual characteristics associated with in situ viral replication or acute inflammation. Terms like hepatitis and encephalitis describe cell damage processes in the setting of inflammation. The latter conditions are accompanied by characteristic, although not diagnostic, signs and symptoms. For example, in the liver, tenderness, enlargement, and jaundice are characteristically present during infection and/or inflammatory disease, while in the brain meningeal pain, seizures, or focal neurologic dysfunction are often characteristically found. With these distinctions clearly in mind, examination of the recent medical literature concerning liver and brain complications of varicella indicate that hepatitis secondary to in situ viral replication or post-infectious inflammation is very rare and encephalitis secondary to in situ viral replication probably never occurs, whereas hepatopathy, encephalopathy, and post-infectious encephalitis are relatively frequently encountered.

Focusing first on the liver, review of clinical, physical, biochemical, and histological aspects of case reports in the literature discloses numerous examples of varicella-associated hepatopathy and hepatoencephalopathy but no examples of primary hepatitis [7–9]. Under the right circumstances, VZV is clearly capable of replication in liver cells. Most commonly, this is encountered in patients who are immunocompromised, but varicella hepatitis with histopathology of focal necrosis has also been reported in immunocompetent patients as well. Virtually all cases have evidence of multiple organ involvement — either disseminated replication of virus in multiple organs or replication in at least one other internal organ, as has been reported in varicella pneumonia with liver involvement. There are no cases, documented by tissue histology, in which the liver is the only internal organ where VZV replicated [1–6].

Nevertheless, there is increasing mention in the literature of "hepatitis" associated with varicella. Landay, Smith et al., and Pitel et al. [13–15] have reported patients with a benign, self-limiting illness consisting of emesis and abnormally elevated levels of liver enzymes but without liver enlargement or tenderness. In these cases, liver biopsies were not done because of the mild nature of each patient's illness. In the present study, 28 of 58 patients with varicella complicated by persistent emesis fall into a similar category, referred to here as hepatopathy. None had an enlarged or tender liver, 24 of 27 had elevated liver enzyme levels at the time of examination (mean SGOT 432, range 17–2780), all remained alert and oriented, and most recovered shortly after hospitalization. Many who had additional liver function assessments demonstrated a variety of transient abnormalities; half of the group tested revealed an abnormal coagulation profile, as well as elevated blood ammonia and lactic acid levels. There were none with low glucose or high bilirubin. As in the reports cited above, there were no liver biopsies performed in this group of patients, however, because of the mild nature of the illness.

In the hepatoencephalopathy group presently reported, 18 patients presented with persistent emesis, elevated liver enzyme levels, and a variety of other abnormalities in liver function as well as definite signs and symptoms of encephalopathy (not encephalitis). In this second category of cases, differing from those with hepatopathy in severity of biochemical derangement and range of target tissue cytotoxicity, there were three patients who had liver biopsies. The liver biopsies demonstrated micro-vacuolar and macrovacuolar fatty metamorphosis and one, in addition, had mild focal periportal lymphocytic infiltrates. None had focal cellular necrosis or cells with intranuclear inclusions consistent with hepatitis or replication of VZV. The major aspect which separates the patients with hepatoencephalopathy from those with hepatopathy is that illness of patients in the former group progressed to include altered mentation and/or behavior. The presence of elevated liver enzymes without other evidence of hepatocellular damage and especially without evidence of inflammation or cellular damage consistent with VZV replication cannot be viewed as hepatitis. The condition is more appropriately viewed as hepatopathy, when only the liver is involved, and hepatoencephalopathy when there is also disordered mentation and behavioral activity.

Turning now to the brain, review of clinical, physical, and histological aspects of case reports in the literature discloses that varicella-associated encephalopathy can be found in numerous instances, virtually always in association with hepatopathy, and varicella-associated encephalitis also appears to be relatively common, although never found in association with in situ VZV replication [17]. Encephalopathy, like hepatopathy, stems from cytotoxic damage to cerebral cortical cells through a process which remains poorly understood. The prominant histologic finding is cellular edema without lymphocytic infiltrates [9]. Spinal fluid exam may reveal increased intracranial pressure but is usually free of pleocytosis. These changes occur in the presence of fatty changes in cells of the liver and kidney and, to a lesser extent, fatty changes in skeletal and heart muscle. The cerebral edema, if not controlled, may be lethal due to caudal displacement of the brain and subsequent constriction of arterial blood supply with hypoxic death of brain cells. Very significantly, however, in patients whose increased intracranial pressure can be controlled, recovery from the cytotoxic event is remarkably free of long-term sequelae [18]. Postmortem examination of brain tissue in those patients who die from hepatoencephalopathy shows no evidence of focal or widespread necrosis, viral inclusions, or lymphocytic infiltrate.

Pitel et al. [15] have conducted a most important prospective study among children

with chickenpox. They have clearly demonstrated that elevated SGOT and SGPT levels are common during the course of chickenpox in children who are experiencing no signs or symptoms of hepatopathy. These findings strongly suggest that there is a continuum of severity relating to the degree of cytotoxicity. The most common condition is the minimal hepatocytotoxicity which occurs in as many as 77 percent of chickenpox cases, without any signs or symptoms referable to liver cell damage. This is followed in severity by the much less common condition referred to here as hepatopathy, which includes patients who develop persistent emesis without disordered mentation or behavior. Finally, the most uncommon and most severe form of cytotoxicity includes patients who not only have hepatopathy but also have encephalopathy. The observation that neither the hepatopathy nor the hepatoencephalopathy which occur in association with chickenpox bears a direct relationship to in situ virus replication suggests that the pathogenesis of these two conditions could be related to alteration of cellular metabolism brought about by virus replication going on elsewhere. Viruses readily shut down the macromolecular events of cells which they infect. There is no particular reason why the effect on cellular metabolism is necessarily limited to the cell actually infected by a virus. Substances could be generated in the infected cell which might influence molecular events in specifically sensitive cells located at some distance from the site of viral replication.

In spite of clear evidence that encephalitis complicates chickenpox, invasion of brain tissue by replicating varicella virus during chickenpox has not been recorded, even in cases where disseminated infection has occurred [17]. Although there are reports of varicella virus replication in brain tissue in association with disseminated zoster infections [19], invasion of brain tissue during primary VZV infection must be extremely rare if it occurs at all. What then is the pathogenesis of the inflammatory cell disease seen in association with chickenpox which results in encephalitis? Death from varicella encephalitis is extremely rare and the few reported cases have been recently reviewed by McKendall and Klawans [17]. The histopathology includes focal areas of demyelination with surrounding areas of microglial proliferation and perivenous mononuclear cell infiltrates. Some cases also include widespread petechial hemorrhage and edema. Due to the lack of a suitable experimental animal model, the pathogenesis of the focal demyelination and occasional widespread vasculitis seen in varicella encephalitis has not been investigated. The described histopathology bears a striking similarity to changes which occur in the brains of animals with experimental allergic encephalomyelitis produced by lymphocytes sensitized to myelin basic protein [20]. Perhaps the pathogenesis of post-infectious varicella encephalitis will turn out to be similar to that found in experimental allergic encephalitis.

In summary, chickenpox appears to commonly cause hepatocytotoxicity, a condition which is usually not associated with symptoms. Rarely, the toxicity proceeds to the level of clinical significance, persistent emesis ensues, and clinical investigation will reveal hepatopathy. In some individuals, clinical symptoms may rapidly proceed to include disordered mentation or behavior, a condition now widely recognized as Reye syndrome. Among a much smaller group of individuals, signs and symptoms of inflammatory intracranial disease can be found. Since viral replication within the respectively involved organs does not appear to occur, the pathogenesis of each condition remains enigmatic. Clearly much remains to be learned from experiments designed to investigate the molecular and host immune responses to infection with varicella zoster virus.

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